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(54) Title: THE COMBINATION OF TOPICAL NASAL MAST CELL STABILIZERS AND TOPICAL NASAL STEROIDS

(57) Abstract

A nasal spray or nasal drops for the treatment of allergic rhinitis is disclosed comprising: a) an effective amount of a topical mast cell stabilizer to inhibit mast cell mediator release where said topical nasal mast cell stabilizer is selected from the group consisting of cromolyn sodium, nedocromil and lodoxamide; b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and c) sterile water.

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THE COMBINATION OF TOPICAL NASAL MAST CELL STABILIZERS AND TOPICAL NASAL STEROIDS

The present invention relates to prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis. More particularly, the present invention relates to the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis by the application of a combination of topical nasal mast cell stabilizers and topical nasal steroids.

BACKGROUND OF THE INVENTION

Seasonal allergic rhinitis is most frequently caused by pollen, pollen fragments and mold spores. The airborne pollens, pollen fragments and mold spores are deposited on the nasal mucosa. In sensitive individuals, rhinitis symptoms develop which include puffy, sore eyes, sneezing, nasal congestion, sinus headaches and fatigue.

The chronic symptoms of perennial allergic rhinitis are most frequently caused by reaction to perennial allergens, such as, house dust mite, mold, cockroach, animal saliva, urine, and dander. The symptoms resemble those of seasonal allergic rhinitis but the duration is year round or episodic depending upon the source of the allergens.

Employed to treat allergic rhinitis are mast cell stabilizers. In response to a challenge by an allergen, mast cells release mediators, which include, histamine, SRS-A, serotonin, adenosine, proteases, etc. which induce vasodilation, smooth muscle contraction, glandular secretion and stimulation of irritant nerve receptors among other symptoms. Mast cell stabilizers inhibit the release of mediators from the mast cells and thereby block the symptoms of their release.

Suitable mast cell stabilizers known or in use today include cromolyn sodium, nedocromil and lodoxamide. Each of these mast cell stabilizers may be topically applied.

Also employed to treat allergic rhinitis are nasal steroids, particularly the corticosteroids. Such steroids have powerful effects on immunologic and hormonal processes and are very effective in treating the inflammation which

accompanies the allergic reaction. Suitable nasal steroids known in use today include beclamethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

SUMMARY OF THE INVENTION

There is provided by the present invention a nasal spray or nasal drops for the treatment of allergic rhinitis comprising:

a) an effective amount of a topical mast cell stabilizer to inhibit mast cell mediator release where said topical nasal mast cell stabilizer is selected from the group consisting of cromolyn sodium, nedocromil and lodoxamide;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

DETAILED DESCRIPTION OF THE INVENTION

The topical nasal mast cell stabilizers herein function by preventing degranulation of mast cells in response to allergens. When allergens are present, they bind to the immunoglobulin on the surface of mast cells and trigger the breakdown, or degranulation, of the cell. Upon degranulation, mast cell components, including mediators for symptoms associated with allergic rhinitis, are released. Person skilled in the art understand that only a sufficient amount of mast cell stabilizer should be administered to inhibit mast cell mediator release and no more. This amount will vary depending on whether cromolyn sodium, nedrocromiol or lodoxamide is employed. In the case of cromolyn sodium, from about 0.5 to about 20 mg, and preferably from about 3 to about 15 mg should be administered in this combination every 4 to 12 hours. In the case of nedocromil, from about 0.1 to about 20 mg, and preferably from about 2 to about 8 mg should be administered every 4 to 12 hours. Likewise, in the case of lodoxamide, from about 0.1 to about 30 mg, and preferably from about 2 to about 15 mg should be administered every 4 to 12 hours. To achieve these dosage ranges, cromolyn sodium should

constitute the nasal spray or nasal drops composition from about 2 to about 80 mg/ml and preferably from about 10 to about 60 mg/ml. Nedocromil should constitute from about 1 to about 80 mg/ml and preferably from about 5 to about 30 mg/ml. Similary, lodoxamide should constitute from about 1 to about 100 mg/ml and preferably from about 5 to about 60 mg/ml.

Cromolyn sodium is also known as disodium cromoglycate or simply "cromolyn". This compound has been marketed under the names Ital and Lomudal (Cox et al., Adv. in Drug Res., 5:115-195 (1970)). Cromolyn is the disodium salt of 1,3-bis-(2-carboxy-chromone-5'-yloxy)-2-hydroxypropane. Cromolyn is believed to interface with the mechanism leading to a transiently elevated $[Ca^{2+}]_i$ upon antigenic stimulation of the cell. Hence, it prevents histamine release. It has also been shown to inhibit degranulation and the antigen-induced $^{45}Ca^{2+}$-influx to a certain degree (Cox, Nature, 216:1328 (1967); Mazurek, et al., Nature, 303:528(1983)). The manufacture of cromolyn is well known and has been described by Fitzmaurice, Lee, Brit. Pat. 1,144, 906.

Nedocromil as used herein inlcudes nedocromil and its pharmaceutically acceptable salts. The preferred salts are the sodium and calcium salts. Nedocromil, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano[3,2-g] guinoline-2,8-dicarboxylic acid, inhibits the release and/or action of pharmacological mediators which result from the *in vivo* combination of certain types of antibodies and specific antigents, e.g. the combination of reaginic antibody with specific antigen (See Example 27 of Brit. Pat 1,292,601). The preparation of nedocromil is described in Brit. Pat. 2022078, U.S. Pat. 4,474,787 and Cairns et al., *J. Med. Chem.* 28, 1832 (1985).

Lodoxamide as used herein includes lodoxamide and its pharmaceutically acceptable salts and esters. The preferred salt of lodoxamide is its di-tris (hydroxymethyl) methyl ammonium (or bis THAM) salt and the preferred ester is the ethyl ester. Lodoxamide is known to inhibit the release of mast cell mediators of inflammation. The manufacture of lodoxamide, N,N'-(2-chloro-5-cyano-m-phenylene) dioxamic acid, is well known and taught in U.S. Pat. 3,962,308 and U.S. Pat. 3,993,679.

The topical nasal steroids for use herein are corticosteroids which inhibit the release of mediators for the symptoms associated with allergic

rhinitis from mast cells and basophils. They also reduce inflammation and suppress neutrophil chemotaxis. The topical nasal steroids herein have relatively few side effects but are known to cause nasal irritation, drying and epistaxis with use of nasal sprays. Thus, persons skilled in the art understand that only a sufficient amount of nasal steroid should be administered to inhibit mast cell mediator release and inflammation and no more. This amount will vary depending on whether beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide is employed. Further, the nasal steroids are relatively long acting and alone can be administered once or twice daily. However, when used in conjunction with an active ingredient requiring more frequent administration, the amount of nasal steroid must be adjusted accordingly. For beclomethasone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the beclomethasone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For flunisolide, from about 30 to about 300 mcg, and preferably from about 50 to about 200 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the flunisolide should constitute of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml, and preferably from about 0.15 to about 0.5 mg/ml. For triamcinolone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the triamcinolone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For dexamethasone, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the dexamethasone should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml. For budesonide, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the budesonide should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml.

The corticosteroid topical nasal steroids are, as a general matter, poorly soluble in water. Thus, they are administered in particulate form, as a micronized suspension in a suitable carrier/solvent system. For the treatment of the lung, it is desirable to produce aerosol particle sizes of less than 3 microns. However, in the instant case where it is desirable to treat nasal symptoms, the necessity of producing an aerosol of small particles is removed. For the present invention, it is only necessary to create a stable suspension of the corticosteroid in water which can be delivered by drops or spray directly into the nasal passages. The particle size of the corticosteroid in suspension is not critical so long as the particle is small enough that the amount of compound available for therapeutic activity is not surface area limited and the particle is stable in suspension. The suspension may be maintained with suitable liposomes. Preferably, however, the suspension is maintained by use of solubilizing agents and a suitable surfactant. Solubilizing agents herein include 1,2-propane diol, 1,3-propane diol, polyethylene glycol having a molecular weight of 100 to 800, dipropylene glycol, or ethanol. A suitable surfactant may be a pharmaceutically acceptable non-ionic, anionic or cationic surfactant. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate or polysorbate 20, fatty acid ethanolamides and their derivatives such as the diethanolamide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually a fatty acids, such as sodium stearate. Organic amine soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminum stearate. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quarternary ammonium compounds such as benzalkonium chloride. Other examples of these and other suitable surfactants can be found in "Pharmaceutical Emulsions and Emulsifying Agents" by Lawrence M. Spatton, second edition; The Chemist and Druggist,

London; "Emulsions' Theory and Practice" by Paul Becher, Reinhold Publishing Corporation, New York; and "Detergents and Emulsifyers, 1969 Annual" by John M. McCutcheon, Morristown, N.J., the disclosures thereof being incorporated herein by reference.

Only sufficient solubilizing agent and surfactant should be employed to stabilize the suspension/emulsion. Generally there should be employed from about 5 to about 30% w/v and preferably from 10 to about 25% w/v of cosolvent. Likewise, there should be employed from about 0.1 to about 10% w/v and preferably from about 0.5 to about 5% w/v of surfactant.

Beclamethasone as used herein includes beclamethasone, beclamethasone acetate, beclamethasone valerate, beclamethasone propionate, beclamethasone dipropionate and the like, including the hydrates thereof. Beclamethose, 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be obtained commercially and is prepared according to Brit. Pat. 912,378 and Brit. Pat. 901,093. Beclamethasone is commercially available.

Flunisolide as used herein includes flunisolide and flunisolide acetate and hydrates thereof. Flunisolide, 6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione, may be prepared using *S. roseochromogenes* as in Brit. Pat. 933,867 and Chem. Abst. 60, 3070f (1964) or using *Cunninghamella blakesleeana* as in U.S. pat. 3,124,571. Flunisolide is also prepared in 4,273,710. Flunisolide is commercially available.

Triamcinolone as used herein includes triamcinolone and its 16-α, 21-diacetate; triamcinolone acetonide, and its 21-acetate, 21-disodium phosphate, and 21-hemisuccinate; triamcinolone benetonide and triamcinolone hexacetonide, including hydrates thereof. Triamcinolene, 9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, may be prepared according to Bernstein et al., *J. Am. Chem. Soc.* 78, 5693 (1956) and 81, 1689 (1959); Thoma et al., *J. Am. Chem. Soc.* 79, 4818 (1957); U.S. Pat. 2,789,118 or U.S. Pat. 3,021,347. Triamcinolone acetonide may be prepared by stirring a suspension of triamcinolone in acetone in the presence of a trace of perchloric acid. Triamcinolone benetonide may be prepared according to Ger. Pat. 2,047,218 or U.S. Pat. 3,749,712. Triamcinolone

hexacetonide may be prepared according to U.S. pat. 3,457,348. The triamcinolone and derivatives as taught herein have been sold or are available commercially.

Dexamethasone as used herein includes dexamethasone and its 21-phosphate, 21-acetate, 21-phosphate disodium salt, 21-dimethylaminoacetate, 21-isonicotinate, 17,21-dipropionate and 21-palmitate. Dexamethasone, (11ß, 16α)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be prepared according to Arth et al., *J. Am. Chem. Soc.* 80, 3161 (1958); Oliveto et al., J. Am. Chem. Soc. 80, 4431 (1958); U.S. Pat. 3,007,923; Ger. Pat. 1,113,690 or Brit. Pat. 869,511. Dexamethasone is commercially available.

Budesonide as used herein includes budesonide and its pharmaceutically acceptable salts. Preferred salts of budesonide include its palmitate, laurate, myristate, stearate, oleate, valerate and acetate salts. Budesonide, 16,17-butylidenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione, is a well known compound and may be prepared according to U.S. Pat. No. 3,929,768, GB Pat. No. 1,429,922, or A. Thalen, R. L. Brattsand, Arzneimittel Forsch. 29, 1787 (1979).

The nasal spray or nasal drop formulation herein can contain, in addition to the compounds discussed above antimicrobial agents, antioxidants, agents to increase viscosity, isotonic agents, buffers, solubilizing agents, surface active agents and the like. Suitable antimicrobial agents include chlorobutanol, phenylmercuric nitrate, phenyl ethyl alcohol, thimerosal, the quaternary ammonium germicides, such as, benzalkonium chloride, benzethonium chloride or cetylpyridium chloride. Suitable antioxidants include sodium sulfite, sodium ascorbate, oxime sulfate, etc. The preferred isotonic agent is sodium chloride however, other isotonic agents such as dextrose, boric acid and sodium tartrate may be employed. The object of the buffer is to adjust the pH to one compatible with nasal mucous membranes and to stabilize the active ingredient. Ideally the target pH should vary between about 4 and about 6.5. Suitable buffers included phthalate buffers, borate buffers, phosphate buffers, such as $HPO_4^{2-}/H_2PO_4^-$, acetate buffers, such as acetic acid/sodium acetate, a bicarbonate buffer such as CO_2/HCO_3, or a citrate buffer, such as citric acid/citrate, also it may be

adjusted by simply adding an acid such as HCl to achieve the desired acidity. Suitable agents to increase viscosity include polyvinyl alcohol, cellulose derivatives, polyvinylpyrollidone, polysorbates or glycerine. Suitable surface active agents improve absorption by the nasal mucosa and include polyoxyl 40 stearate, polyoxyethylene 50 stearate, polysorbate 80 and octoxynol.

In general, the concentration of the additives will be in the range as follows:

Additive	% W/V
antimicrobial agent	0.001 - 2.0
antioxidant	0.01 - 0.20
isotonic agent	0.01 - 0.50
solubilizing agents	0.01 - 1.0
viscosity builders	0.1 - 2.0
surface active agents	0.01 - 1.0

The buffer should be added in sufficient amount to achieve the pH range stated above of about 4.0 to about 6.5.

Aerosol formulations and nose drops are prepared as per known techniques. The water employed should be of an appropriate pharmacutical grade of purified water. These formulations should be administered by drop or spray every 4 to 6 hours to obtain the desired relief.

WHAT IS CLAIMED IS:

1. A nasal spray or nasal drops formulation comprising:

a) an effective amount of a topical mast cell stabilizer to inhibit mast cell mediator release where said topical nasal mast cell stabilizer is selected from the group consisting of cromolyn sodium, nedocromil and lodoxamide;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

2. The formulation of claim 1 wherein said mast cell stabilizer is cromolyn sodium and said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

3. The formulation of claim 1 wherein said mast cell stabilizer is nedocromil and said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

4. The formulation of claim 1 wherein said mast cell stabilizer is lodoxamide and said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

5. The formulation of claim 1 wherein said cromolyn sodium constitutes of the nasal spray or nasal drops composition from about 2 to about 80 mg/ml; said nedocromil constitutes of the nasal spray or nasal drops composition from about 1 to about 80 mg/ml and said lodoxamide constitutes of the nasal spray or nasal drops composition from about 1 to about 100 mg/ml.

6. The formulation of claim 1 wherein said beclomethasone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml; said flunisolide constitutes of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml; said triamcinolone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5

mg/ml; said dexamethasone constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml; and said budesonide constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/58 A61K31/57 //(A61K31/58,31:47),(A61K31/58,31:35), (A61K31/58,31:275),(A61K31/57,31:47),(A61K31/57,31:35), (A61K31/57,31:275)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DATABASE WPI Section Ch, Week 7847 Derwent Publications Ltd., London, GB; Class B05, AN 78-85280A XP002019330 ANONYMOUS: "Di:sodium cromoglycate or cromoglycic acid - useful in pharmaceutical compsns., food additives and colourings" see abstract & RESEARCH DISCLOSURE, vol. 175, no. 046, 10 November 1978, EMSWORTH, GB, --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP,A,0 241 134 (FISONS PLC) 14 October 1987 see claims 1,2,8-10	1-6
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DR. W. FORTH ET AL.: "Allgemeine und spezielle Pharmakologie und Toxikologie" 1983 , BIBLIOGRAPHISCHES INSTITUT , MANNHEIM XP002019328 see page 184 - page 186 ---	1-6
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/10849

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		NL-A-	8204013	16-05-83
		SE-B-	454356	25-04-88
		SE-A-	8205904	18-10-82
		US-A-	4866051	12-09-89